Research Article

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CP-MLR DIRECTED QSAR RATIONALES FOR THE ACTIVITY PROFILE OF (PHENYLPIPERAZINYL-ALKYL) OXINDOLES AS 5-HT₇ RECEPTOR LIGANDS

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Received on: 03/04/15 Revised on: 18/05/15 Accepted on: 08/06/15

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DOI: 10.7897/2277-4343.064100

ABSTRACT

The 5-HT₇ receptor binding affinities of the oxindole derivatives have been quantitatively analyzed in terms of Dragon descriptors. The derived QSAR models have provided rationales to explain the binding affinity of titled compounds. In order to improve the 5-HT₇ receptor binding affinity of a compound higher value of molecular topology and symmetry accounting parameter path/walk 2- Randic shape index (descriptor PW2) and lower value of eigenvector coefficient sum from adjacency matrix (descriptor VEA1) are favorable. Presence of more number of sp³ hybridized secondary carbon atoms (descriptor nCs) and secondary aliphatic amides (descriptor nCONHR) in a molecule will be supportive to the activity. The associations of masses to the eigenvalue n.4 of Burden matrix (BEHm4), van der Waals volume to path length 2 of Geary autocorrelation (GATS2v) and Sanderson electronegativity to path length 6 of Moran autocorrelation (MATS6e) and path length 4 of Geary autocorrelation (GATS4e) have shown the prevalence of atomic properties and charge content in terms of 9th and 5th order topological and mean topological charge indices (GGI9 and JGI5) to explain the binding affinity. The PLS analysis has also confirmed the dominance of information content of the CP-MLR identified descriptors. The derived models and participating descriptors in them have suggested that the substituents of oxindole moiety have sufficient scope for further modification.

Keywords: QSAR, (phenylpiperazinyl-alkyl)oxindoles, 5-HT₇ receptor ligands, binding affinity, combinatorial protocol in multiple linear regression (CP-MLR), partial least squares (PLS) analysis.

INTRODUCTION

5-hydroxytryptamine₇ (5-HT₇) receptor, the member of serotonin subfamily of G-protein coupled receptors^{1,2} has implications in many CNS functions and disorders, like schizophrenia³, depression⁴⁻⁷, epilepsy⁸, migraine^{9,10} and control of circadian rhythm^{11,12}. Thus, renders it as a novel drug target to cure such ailments. Only a few compounds have been reported, in recent years, as antagonists¹³⁻¹⁸, selective agonists^{15,19}, nonselective agonists^{20,21} and partial agonists^{15,19,22} at the 5-HT₇ receptor. However, the use of some of the potent compounds was limited due to strong side effects such as blood pressure and heart rate changes²⁰ or poor experimental metabolic stability. The representative chemical species showing metabolic stability and selectivity at 5-HT₇ receptor include tetrahydrobenzindoles²³, (2-methoxyphenyl)piperazinyls²⁴, DR4365²⁵, DR4446²⁶ and DR4485²⁷. A synthetic study, with the aim to obtain compounds having strong 5-HT₇ receptor affinity and good selectivity over other receptors, was performed by Volk *et al.*²⁸. In view of the importance of 5-HT₇ antagonists in the clinical management of several disorders, a quantitative structure–activity relationship is attempted on the binding affinities of these oxindole derivatives. The aim of present communication is to establish quantitative SAR (QSAR) between biological activity and descriptors unfolding the structural variations of the reported oxindole derivatives.

MATERIALS AND METHODS**Chemical structure database and biological activity**

This study comprises a chemical structure database of reported forty one oxindole derivatives. The biological effects, reported as K_i, represents the radioligand binding of [³H]LSD (NEN) on cloned human serotonin receptor subtype 7 (h5-HT₇) produced in CHO cells. In present study, for a given compound, it is expressed as pK_i on a molar basis. The structural variations and the binding affinities of titled compounds have been given in Table 1. The reported activity data has been used for subsequent QSAR analyses as the response variables. For the purpose of modeling all 41 analogues have been divided into training and test sets. Initial examination of data set revealed that compound no. 27 behaves differently thus this and another compound 30 (Table 1) whose biological effects were not determined are not part of the data set. Out of the remaining 39 analogues, nearly one fourth compounds (09) have been placed in the test set for the validation of derived models. The training and test set compounds are also listed in Table 1.

Theoretical molecular descriptors

The structures of the compounds under study have been drawn in 2D ChemDraw²⁹. The drawn structures were then converted into 3D modules using the default conversion procedure implemented in the CS Chem3D

Ultra. The energy of these 3D-structures was minimized in the MOPAC module using the AM1 procedure for closed shell systems. This will ensure a well defined conformer relationship among the compounds of the study. All these energy minimized structures of respective compounds have been ported to DRAGON software³⁰ for the computation of descriptors for the titled compounds mentioned in Table 1. This software offers several hundreds of descriptors from different perspectives corresponding to 0D-, 1D-, and 2D-descriptor modules. The outlined modules comprised of ten different classes, namely, the constitutional (CONST), the topological (TOPO), the molecular walk counts (MWC), the BCUT descriptors (BCUT), the Galvez topological charge indices (GALVEZ), the 2D autocorrelations (2D-AUTO), the functional groups (FUNC), the atom-centered fragments (ACF), the empirical descriptors (EMP), and the properties describing descriptors (PROP). For each of these classes the DRAGON software computes a large number of descriptors which are characteristic to the molecules under multi-descriptor environment. The definition and scope of these descriptor's classes is given in Table 2. The combinatorial protocol in multiple linear regression³¹ and partial least-squares³²⁻³⁴ procedures has been used in the present work for developing QSAR models. Before the application of CP-MLR procedure, all those descriptors which are intercorrelated beyond 0.90 and showing a correlation of less than 0.1 with the biological endpoints (descriptor vs. activity, $r < 0.1$) were excluded. This has reduced the total dataset of the compounds from 491 to 88 descriptors as relevant ones for the binding activity. A brief description of the computational procedure is given below.

Model development

The combinatorial protocol in multiple linear regression (CP-MLR) is a 'filter' based variable selection procedure for model development in QSAR studies. Its procedural aspects and implementations are discussed in our publications³⁵⁻⁴⁰. It involves selected subset regressions. In this procedure a combinatorial strategy with appropriately placed 'filters' has been interfaced with MLR to result in the extraction of diverse structure-activity models, each having unique combination of descriptors from the dataset under study. In this, the contents and number of variables to be evaluated are mixed according to the predefined confines. Here the 'filters' are significance evaluators of the variables in regression at different stages of model development. Of these, filter-1 is set in terms of inter-parameter correlation cutoff criteria for variables to stay as a subset (filter-1, default value 0.3 and upper limit ≤ 0.79). In this, if two variables are correlated higher than a predefined cutoff value the respective variable combination is forbidden and will be rejected. The second filter is in terms of t-values of regression coefficients of variables associated with a subset (filter-2, default value 2.0). Here, if the ratio of regression coefficient and associated standard error of any variable is less than a predefined cutoff value then the variable combination will be rejected. Since successive additions of variables to multiple regression equation will

increase successive multiple correlation coefficient (r) values, square-root of adjusted multiple correlation coefficient of regression equation, $\bar{r}$, has been used to compare the internal explanatory power of models with different number of variables. Accordingly, a filter has been set in terms of predefined threshold level of $\bar{r}$ -bar (filter-3, default value 0.71) to decide the variables' 'merit' in the model formation. Finally, to exclude false or artificial correlations, the external consistency of the variables of the model have been addressed in terms of cross-validated R^2 or Q^2 criteria from the leave-one-out (LOO) cross-validation procedure as default option (filter-4, default threshold value $0.3 \leq Q^2 \leq 1.0$). All these filters make the variable selection process efficient and lead to unique solution. In order to collect the descriptors with higher information content and explanatory power, the threshold of filter-3 was successively incremented with increasing number of descriptors (per equation) by considering the $\bar{r}$ -bar value of the preceding optimum model as the new threshold for next generation.

Model validation

In this study, the data set is divided into training set for model development and test set for external prediction. Goodness of fit of the models was assessed by examining the multiple correlation coefficient (r), the standard deviation (s), the F-ratio between the variances of calculated and observed activities (F). A number of additional statistical parameters such as the Akaike's information criterion, AIC^{41,42}, the Kubinyi function, FIT^{43,44}, and the Friedman's lack of fit, LOF⁴⁵ (Eqs. 1-3) have also been derived to evaluate the best model.

$$AIC = \frac{RSS \times (n + p')}{(n - p')^2} \quad (1)$$

$$FIT = \frac{r^2 \times (n - k - 1)}{(n + k^2) \times (1 - r^2)} \quad (2)$$

$$LOF = \frac{\frac{RSS}{n}}{\left[1 - \frac{k(d+1)}{n}\right]^2} \quad (3)$$

Where, RSS is the sum of the squared differences between the observed and the estimated activity values, k is the number of variables in the model, p' is the number of adjustable parameters in the model, and d is the smoothing parameter. The AIC takes into account the statistical goodness of fit and the number of parameters that have to be estimated to achieve that degree of fit. The FIT, closely related to the F-value (Fisher ratio), was proved to be a useful parameter for assessing the quality of the models. The main disadvantage of the F-value is its sensitivity to changes in k (the number of variables in the equation, which describe the model), if k is small, and its lower sensitivity if k is large. The FIT criterion has a low sensitivity toward changes in k-values, as long as they are small numbers, and a substantially increasing sensitivity

for large k-values. The model that produces the minimum value of AIC and the highest value of FIT is considered potentially the most useful and the best. The LOF takes into account the number of terms used in the equation and is not biased, as are other indicators, toward large numbers of parameters. A minimum LOF value infers that the derived model is statistically sound.

The internal validation of derived model was ascertained through the cross-validated index, Q^2 , from leave-one-out and leave-five-out procedures. The LOO method creates a number of modified data sets by taking away one compound from the parent data set in such a way that each observation has been removed once only. Then one model is developed for each reduced data set, and the response values of the deleted observations are predicted from these models. The squared differences between predicted and actual values are added to give the predictive residual sum of squares, PRESS. In this way, PRESS will contain one contribution from each observation. The cross-validated Q^2_{LOO} value may further be calculated as

$$Q^2_{LOO} = 1 - \text{PRESS} / \text{SSY} \quad (4)$$

Where, SSY represents the variance of the observed activities of molecules around the mean value. In leave-five-out procedure, a group of five compounds is randomly kept outside the analysis each time in such a way that all the compounds, for once, become the part of the predictive groups. A value greater than 0.5 of Q^2 -index hints toward a reasonable robust model.

The external validation or predictive power of derived model is based on test set compounds. The squared correlation coefficient between the observed and predicted values of compounds from test set, r^2_{Test} , has been calculated as

$$r^2_{\text{Test}} = 1 - \frac{\sum (Y_{\text{Pred}(\text{Test})} - Y_{(\text{Test})})^2}{\sum (Y_{(\text{Test})} - \bar{Y}_{(\text{Training})})^2} \quad (5)$$

Where, $Y_{\text{Pred}(\text{Test})}$ and $Y_{(\text{Test})}$ indicate predicted and observed activity values, respectively of the test-set compounds, and $\bar{Y}_{(\text{Training})}$ indicate mean activity value of the training set. r^2_{Test} is the squared correlation coefficient between the observed and predicted data of the test-set. A value greater than 0.5 of r^2_{Test} suggests that the model obtained from training set has a reliable predictive power.

Y-randomization

Chance correlations, if any, associated with the CP-MLR models were recognized in randomization test^{46,47} by repeated scrambling of the biological response. The data sets with scrambled response vector have been reassessed by multiple regression analysis (MRA). The resulting regression equations, if any, with correlation coefficients better than or equal to the one corresponding to the

unscrambled response data were counted. Every model has been subjected to 100 such simulation runs. This has been used as a measure to express the percent chance correlation of the model under scrutiny.

RESULTS AND DISCUSSION

In multi-descriptor class environment, exploring for best model equation(s) along the descriptor class provides an opportunity to unravel the phenomenon under investigation. In other words, the concepts embedded in the descriptor classes relate the biological actions revealed by the compounds. For the purpose of modeling study, 09 compounds have been included in the test set for the validation of the models derived from 30 training set compounds. A total number of 88 significant descriptors from 0D-, 1D- and 2D-classes have been subjected to CP-MLR analysis with default 'filters' set in it. Statistical models in three, four and five descriptors have been derived successively to achieve the best relationship correlating 5-HT₇ binding affinity. These models (with 88 descriptors) were identified in CP-MLR by successively incrementing the filter-3 with increasing number of descriptors (per equation). For this the optimum r-bar value of the preceding level model has been used as the new threshold of filter-3 for the next generation. The selected models in four and five descriptors are presented below.

$$\begin{aligned} pK_i &= 2.313(0.593)PW2 - 2.423(0.484)GGI9 \\ &+ 3.382(0.630)nCs + 2.001(0.736)nCONHR + 6.612 \\ n &= 30, r = 0.784, s = 0.391, F = 10.014, FIT = 0.870, \\ LOF &= 0.236, AIC = 0.214, \\ Q^2_{LOO} &= 0.395, Q^2_{LSO} = 0.478, r^2_{\text{randY}(\text{sd})} = 0.118(0.071), \\ r^2_{\text{Test}} &= 0.502 \end{aligned} \quad (6)$$

$$\begin{aligned} pK_i &= 2.933(0.522)PW2 - 2.677(0.408)GGI9 - \\ &1.058(0.301)MATS6e + 3.318(0.522)nCs \\ &+ 1.663(0.617)nCONHR + 7.007 \\ n &= 30, r = 0.863, s = 0.324, F = 14.116, FIT = 1.283, \\ LOF &= 0.189, AIC = 0.157, \\ Q^2_{LOO} &= 0.623, Q^2_{LSO} = 0.614, r^2_{\text{randY}(\text{sd})} = 0.179(0.085), \\ r^2_{\text{Test}} &= 0.522 \end{aligned} \quad (7)$$

$$\begin{aligned} pK_i &= 0.851(0.256)T(O..F) - 1.650(0.332)BEHm4 \\ &+ 3.045(0.424)BELm5 - 1.071(0.364)GGI9 - \\ &3.154(0.446)GATS5p + 9.449 \\ n &= 30, r = 0.861, s = 0.326, F = 13.833, FIT = 1.257, \\ LOF &= 0.192, AIC = 0.160, \\ Q^2_{LOO} &= 0.575, Q^2_{LSO} = 0.546, r^2_{\text{randY}(\text{sd})} = 0.170(0.086), \\ r^2_{\text{Test}} &= 0.574 \end{aligned} \quad (8)$$

$$\begin{aligned} pK_i &= 4.192(0.576)PW2 - 0.855(0.330)BEHm4 - \\ &2.524(0.423)GGI9 - 0.951(0.313)MATS6e \\ &+ 3.433(0.542)nCs + 7.199 \\ n &= 30, r = 0.861, s = 0.327, F = 13.801, FIT = 1.254, \\ LOF &= 0.192, AIC = 0.160, \\ Q^2_{LOO} &= 0.586, Q^2_{LSO} = 0.528, r^2_{\text{randY}(\text{sd})} = 0.146(0.084), \\ r^2_{\text{Test}} &= 0.592 \end{aligned} \quad (9)$$

$$\begin{aligned}
 \text{pK}_i &= 4.071(0.564)\text{PW2} - 2.470(0.436)\text{GGI9} - 1.289(0.306)\text{MATS6e} + 1.068(0.433)\text{GATS2v} \\
 &+ 3.302(0.534)\text{nCs} + 6.563 \\
 n &= 30, r = 0.858, s = 0.330, F = 13.405, \text{FIT} = 1.218, \\
 \text{LOF} &= 0.196, \text{AIC} = 0.163, \\
 Q^2_{\text{LOO}} &= 0.533, Q^2_{\text{LSO}} = 0.557, r^2_{\text{randY}}(\text{sd}) = 0.172(0.094), \\
 r^2_{\text{Test}} &= 0.597 \quad (10)
 \end{aligned}$$

In above regression equations, the values given in the parentheses are the standard errors of the regression coefficients. The $r^2_{\text{randY}}(\text{sd})$ is the mean random squared multiple correlation coefficient of the regressions in the activity (Y) randomization study with its standard deviation from 100 simulations. In the randomization study (100 simulations per model), none of the identified models has shown any chance correlation. The signs of the regression coefficients suggest the direction of influence of explanatory variables in the models.

The participated descriptors PW2 and T(O..F) are from the TOPO class of Dragon descriptors. The TOPO class descriptors are based on a graph representation of the molecule and are numerical quantifiers of molecular topology obtained by the application of algebraic operators to matrices representing molecular graphs and whose values are independent of vertex numbering or labeling. They can be sensitive to one or more structural features of the molecule such as size, shape, symmetry, branching and cyclicity and can also encode chemical information concerning atom type and bond multiplicity. The descriptor PW2 is Path/walk 2- Randic shape index and descriptor T(O..F) is the sum of topological distances between O and F. The positive correlation of descriptors PW2 and T(O..F) to the activity advocates that higher values of these descriptors would be beneficiary to activity.

The descriptors MATS6e, GATS5p and GATS2v belong to the 2D-AUTO class. The 2D-AUTO descriptors have their origin in autocorrelation of topological structure of Broto-Moreau (ATS), of Moran (MATS) and of Geary (GATS). The computation of these descriptors involves the summation of different autocorrelation functions corresponding to the different fragment lengths and lead to different autocorrelation vectors corresponding to the lengths of the structural fragments. Also a weighting component in terms of a physicochemical property has been embedded in these descriptors. As a result, these descriptors address the topology of the structure or parts thereof in association with a selected physicochemical property. In these descriptors' nomenclature, the penultimate character, a number, indicates the number of consecutively connected edges considered in its computation and is called as the autocorrelation vector of lag k (corresponding to the number of edges in the unit fragment). The very last character of the descriptor's nomenclature indicates the physicochemical property considered in the weighting component for its computation. The participated descriptor GATS2v (Geary autocorrelation - lag 2 weighted by atomic van der Waals volumes) correlated positively to the activity. The other descriptors emerged in above models from this class,

MATS6e (Moran autocorrelation - lag 6 weighted by atomic Sandersons electronegativities) and GATS5p (Geary autocorrelation - lag 5 weighted by atomic polarizabilities) have shown negative correlation to the activity. The positive correlation suggest the favorable conditions associated with lag 2 weighted by atomic van der Waals volumes and negative correlation unfavorable conditions with lag 6 weighted by atomic Sandersons electronegativities and lag 5 weighted by atomic polarizabilities.

Descriptors BEHm4 and BELm5 are BCUT class descriptors. The BCUT descriptors are the first 8 highest and the lowest absolute eigenvalues, BEHwk and BELwk, respectively, for the modified Burden adjacency matrix. Here w refers to the atomic property and k to the eigenvalue rank. The ordered sequence of the highest and the lowest eigen values reflect upon the relevant aspects of molecular structure, useful for similarity searching. The signs of regression coefficients of BCUT descriptors BEHm4 (the highest eigenvalue n.4 of Burden matrix/weighted by atomic masses) and BELm5 (the lowest eigenvalue n.5 of Burden matrix/weighted by atomic masses) delineate that a lower value of descriptor BEHm4 and a higher value of descriptor BELm5 is advantageous for activity.

The descriptor GGI9 belongs to GALVEZ class of Dragon descriptors. GALVEZ descriptors are the Galvez topological charge indices and have their origin in the first ten eigenvalues of the polynomial of corrected adjacency matrix of the compounds. All the GALVEZ class descriptors belong to two categories. Of this one category corresponds to the topological charge index of order n (GGIn) and the other to the mean topological charge index of order n (JGIn), where 'n' represents the order of eigenvalue. The descriptor GGI9 (topological charge index of order 9) have shown negative correlation to the activity suggesting that a lower value of it would augment the 5-HT₇ binding activity of titled compounds.

The remaining participated descriptors nCs and nCONHR, in above models belongs to FUNC class. The functional class descriptors are molecular descriptors based on the counting of the chemical functional groups. The descriptor nCs represents the number of total sp³ hybridized secondary carbon atoms. Descriptor nCONHR accounts for the number of secondary aliphatic amides. The positive contribution of both of these descriptors, nCs and nCONHR, to the activity recommends more number of sp³ hybridized secondary carbon atoms and secondary aliphatic amides in a molecule for elevated binding affinity of titled compounds.

The models discussed above could estimate 74.47 percent variance in observed activity of the compounds. Considering the number of observation in the dataset, models with up to six descriptors were explored. A total number of 05 models, sharing 10 descriptors among them, were obtained through CP-MLR. The given below are all six-descriptor models for the activity. These models have

accounted for up to 81.72 percent variance in the observed activities.

$$\begin{aligned} pK_i = & 3.702(0.519)PW2 - 0.851(0.283)BEHm4 - \\ & 2.388(0.366)GGI9 - 0.827(0.271)MATS6e \\ & + 3.803(0.480)nCs + 1.654(0.535)nCONHR + 6.507 \\ n = & 30, r = 0.904, s = 0.280, F = 17.197, FIT = 1.563, \\ LOF = & 0.167, AIC = 0.126, \\ Q^2_{LOO} = & 0.722, Q^2_{LSO} = 0.712, r^2_{randY(sd)} = 0.209(0.105), \\ r^2_{Test} = & 0.633 \end{aligned} \quad (11)$$

$$\begin{aligned} pK_i = & 4.058(0.502)PW2 - 2.385(0.369)GGI9 - \\ & 1.817(0.433)JGI5 - 0.724(0.296)MATS6e - \\ & 1.118(0.356)GATS4e + 4.154(0.523)nCs + 7.791 \\ n = & 30, r = 0.903, s = 0.282, F = 16.956, FIT = 1.541, \\ LOF = & 0.169, AIC = 0.128, \\ Q^2_{LOO} = & 0.692, Q^2_{LSO} = 0.695, r^2_{randY(sd)} = 0.200(0.101), \\ r^2_{Test} = & 0.518 \end{aligned} \quad (12)$$

$$\begin{aligned} pK_i = & 3.530(0.573)PW2 - 2.432(0.403)GGI9 - \\ & 1.163(0.288)MATS6e + 0.836(0.413)GATS2v \\ & + 3.531(0.503)nCs + 1.362(0.600)nCONHR + 6.239 \\ n = & 30, r = 0.885, s = 0.305, F = 13.964, FIT = 1.269, \\ LOF = & 0.198, AIC = 0.149, \\ Q^2_{LOO} = & 0.637, Q^2_{LSO} = 0.615, r^2_{randY(sd)} = 0.212(0.091), \\ r^2_{Test} = & 0.630 \end{aligned} \quad (13)$$

$$\begin{aligned} pK_i = & 3.614(0.597)PW2 - 2.623(0.385)GGI9 - \\ & 0.780(0.388)JGI5 - 0.759(0.320)MATS6e \\ & + 3.728(0.533)nCs + 1.351(0.602)nCONHR + 6.827 \\ n = & 30, r = 0.885, s = 0.305, F = 13.918, FIT = 1.265, \\ LOF = & 0.198, AIC = 0.150, \\ Q^2_{LOO} = & 0.631, Q^2_{LSO} = 0.627, r^2_{randY(sd)} = 0.184(0.082), \\ r^2_{Test} = & 0.504 \end{aligned} \quad (14)$$

$$\begin{aligned} pK_i = & 4.034(0.529)PW2 - 1.007(0.481)VEA1 - \\ & 2.070(0.450)GGI9 - 1.025(0.313)MATS6e \\ & + 0.855(0.418)GATS2v + 3.404(0.502)nCs + 6.608 \\ n = & 30, r = 0.882, s = 0.309, F = 13.479, FIT = 1.225, \\ LOF = & 0.203, AIC = 0.154, \\ Q^2_{LOO} = & 0.636, Q^2_{LSO} = 0.639, r^2_{randY(sd)} = 0.209(0.104), \\ r^2_{Test} = & 0.533 \end{aligned} \quad (15)$$

In the randomization study (100 simulations per model), none of the identified models has shown any chance correlation. The values greater than 0.5 of Q^2 -index is in accordance to a reasonable robust QSAR model. The pK_i values of training set compounds calculated using Equations (11) to (15) have been included in Table 3. These models are validated with an external test set of nine compounds listed in Table 1. The predictions of the test set compounds based on external validation are found to be satisfactory as reflected in the test set r^2 (r^2_{Test}) values and the predicted activity values are also reported in Table 3. The plot showing goodness of fit between observed and calculated activities for the training and test set compounds is given in Figure 1.

The descriptors PW2, BEHm4, GGI9, MATS6e, GATS2v, nCs and nCONHR which were emerged in models discussed earlier, have once again shown their importance in six parameter models and convey same inferences to the activity. The newly emerged descriptors are JGI5 (a GALVEZ class descriptor), GATS4e (a 2D-AUTO class descriptor) and VEA1 (a TOPO class descriptor). All these descriptors, JGI5 (the mean topological charge index of order 5), GATS4e (Geary autocorrelation - lag 4 weighted by atomic Sandersons electronegativities) and VEA1 (eigenvector coefficient sum from adjacency matrix) have shown negative correlation to the activity suggesting that a lower value of these descriptors would be beneficiary to the activity.

A PLS (partial least squares) analysis has been carried out on the 10 CP-MLR identified descriptors (Table 4) to facilitate the development of a 'single window' structure-activity model and to identify their (descriptors) potential in explaining the 5-HT₇ receptor binding affinities of oxindole derivatives. It also gives an opportunity to make a comparison of the relative significance among the descriptors. The fraction contributions obtainable from the normalized regression coefficients of the descriptors allow this comparison within the modeled activity. For the purpose of PLS, the descriptors have been autoscaled (zero mean and unit s.d.) to give each one of them equal weight in the analysis. In the PLS cross-validation, five components are found to be the optimum for these 10 descriptors and they explained 79.92% variance in the activity.

The MLR-like PLS coefficients of these descriptors are given in Table 4. The calculated activity values of training and test set compounds are in close agreement to that of the observed ones and are listed in Table 3. For the sake of comparison, the plot showing goodness of fit between observed and calculated activities (through PLS analysis) for the training and test set compounds is given in Figure 1. Figure 2 shows a plot of the fraction contribution of normalized regression coefficients of these descriptors to the activity.

The PLS analysis has also suggested PW2 (a TOPO class descriptor) as the most determining descriptor for modeling the activity of the compounds. The other nine descriptors in decreasing order of significance are nCs, GGI9, VEA1, BEHm4, MATS6e, nCONHR, JGI5, GATS4e and GATS2v (Table 4; Figure 2). All these descriptors are part of Equations 6-15 and convey same inference in the PLS model as well. It is also observed that PLS model from the dataset devoid of 10 descriptors mentioned in Table 4 is inferior in explaining the activity of the analogues.

Table 1: Structures and reported 5-HT₇ receptor binding affinity of (phenylpiperaziny-alkyl)oxindole derivatives

Cpd.	R ₁	R ₂	R ₃	n	NR ₄ R ₅	K _i (nM) ^a
1	H	H	Et	3		21
2	H	H	Et	4		0.41
3	H	H	Et	5		1.45
4	H	H	Et	4		0.38
5	H	H	Et	5		1.24
6 ^b	H	H	Et	4		2.07
7	H	Me	Et	4		33.38
8	H	H	Et	4		5.38
9	H	Bn	Et	4		6.57
10	5-F	H	Et	4		2.11
11	5-F	H	H	4		1.96
12 ^b	5-F	H	Et	4		1.5
13	5-F	H	H	4		3.4

14	H	H	<i>i</i> -Bu	4		1.8
15 ^b	H	H	H	4		0.49
16 ^b	H	H	H	4		7
17	5-F	H	H	4		44
18 ^b	H	H	Et	4		2.55
19	H	H	Et	4		25.4
20	H	H	Et	4		5.11
21	H	H	Et	4		0.43
22	H	H	Et	4		0.63
23	H	H	Et	4		0.6
24	H	H	Et	4		0.66
25	H	H	Et	4		1.02
26 ^b	H	H	Et	4		1.19
27 ^c	H	H	Et	4		5.3
28	H	H	Et	4		4.31
29	H	H	Et	4		7.65
30	H	H	Et	4		- ^d

31	5-Cl	H	Et	4		8.27
32 ^b	6-F	H	Et	4		0.67
33	5-Cl,6-F	H	Et	4		9.07
34	5-F,7-Cl	H	Et	4		4.75
35 ^b	5-Cl,7-Cl	H	Et	4		9.46
36 ^b	5-F	H	Et	4		2.81
37	5-Cl	H	Et	4		3.72
38	6-F	H	Et	4		0.79
39	5-Cl,6-F	H	Et	4		6.99
40	5-F,7-Cl	H	Et	4		5.97
41	5-Cl,7-Cl	H	Et	4		10.13

^aRef. [28]; ^bTest set compounds; ^cOutlier; ^dNot determined.**Table 2: Dragon descriptor classes^a used along with their definition and scope for modeling the binding affinity**

Descriptor class (acronyms)	Definition and scope
Constitutional (CONST)	Dimensionless or 0D descriptors; independent from molecular connectivity and conformations
Topological (TOPO)	2D-descriptor from molecular graphs and independent conformations
Molecular walk counts (MWC)	2D-descriptors representing self-returning walks counts of different lengths
Modified Burden eigenvalues (BCUT)	2D-descriptors representing positive and negative eigenvalues of the adjacency matrix, weights the diagonal elements and atoms
Galvez topological charge indices (GALVEZ)	2D-descriptors representing the first 10 eigenvalues of corrected adjacency matrix
2D-autocorrelations (2D-AUTO)	Molecular descriptors calculated from the molecular graphs by summing the products of atom weights of the terminal atoms of all the paths of the considered path length (the lag)
Functional groups (FUNC)	Molecular descriptors based on the counting of the chemical functional groups
Atom centered fragments (ACF)	Molecular descriptors based on the counting of 120 atom centered fragments, as defined by Ghose-Crippen
Empirical (EMP)	1D-descriptors represent the counts of non-single bonds, hydrophilic groups and ratio of the number of aromatic bonds and total bonds in an H-depleted molecule
Properties (PROP)	1D-descriptors representing molecular properties of a molecule

^aReference [30].

Table 3: Observed and modeled 5-HT₇ receptor binding affinity of (phenylpiperazinyl-alkyl)oxindole derivatives

Cpd.	pKi						
	Obsd ^a .	Eq. (11)	Eq. (12)	Eq. (13)	Eq. (14)	Eq. (15)	PLS
1	7.68	7.66	7.37	7.44	7.51	7.45	7.66
2	9.39	9.05	9.09	9.06	9.10	9.01	9.02
3	8.84	8.84	8.90	8.96	8.81	9.01	9.04
4	9.42	8.98	8.97	8.92	9.05	8.92	8.94
5	8.91	8.78	8.79	8.82	8.77	8.93	8.96
6 ^b	8.68	8.55	8.45	8.75	8.73	8.57	8.41
7	7.48	7.47	7.58	7.44	7.57	7.98	7.65
8	8.27	8.09	7.95	7.99	8.17	7.83	8.08
9	8.18	8.19	8.18	8.22	8.09	8.15	8.07
10	8.68	8.68	8.50	8.64	8.45	8.62	8.68
11	8.71	8.34	8.43	8.39	8.24	8.39	8.42
12 ^b	8.82	8.72	8.57	8.81	8.47	8.83	8.70
13	8.47	8.36	8.42	8.54	8.23	8.60	8.41
14	8.74	8.86	8.81	9.13	8.89	8.74	8.56
15 ^b	9.31	8.72	8.99	8.92	8.83	8.82	8.81
16 ^b	8.15	8.58	8.81	8.70	8.74	8.67	8.67
17	7.36	7.77	7.92	7.99	7.80	7.89	7.81
18 ^b	8.59	8.46	8.39	8.46	8.45	8.30	8.52
19	7.6	7.99	7.87	7.87	7.98	7.82	8.11
20	8.29	8.77	8.85	8.70	8.91	8.64	8.67
21	9.37	8.99	9.16	9.08	9.02	9.10	8.97
22	9.2	9.38	9.37	9.12	9.29	9.24	9.44
23	9.22	9.35	9.47	9.25	9.24	9.38	9.42
24	9.18	9.57	9.25	9.43	9.45	9.52	9.54
25	8.99	8.95	8.90	8.93	9.05	8.94	8.90
26 ^b	8.92	8.98	9.13	9.10	9.02	9.11	8.96
27 ^c	8.28	9.02	9.21	9.36	9.06	9.37	8.99
28	8.37	8.57	8.59	8.28	8.58	8.36	8.40
29	8.12	8.03	7.96	7.90	7.97	7.96	7.92
30	- ^d	9.44	9.02	9.31	9.09	9.29	9.15
31	8.08	8.26	8.39	8.50	8.49	8.46	8.36
32 ^b	9.17	8.91	8.85	8.78	8.78	8.73	8.85
33	8.04	8.35	8.26	8.41	8.34	8.32	8.31
34	8.32	8.08	8.23	8.23	8.07	8.13	8.07
35 ^b	8.02	8.04	8.12	8.11	8.11	8.00	8.03
36 ^b	8.55	8.67	8.46	8.57	8.46	8.59	8.66
37	8.43	8.20	8.30	8.38	8.46	8.39	8.29
38	9.1	8.90	8.81	8.71	8.78	8.70	8.83
39	8.16	8.32	8.24	8.34	8.34	8.30	8.27
40	8.22	8.06	8.20	8.16	8.07	8.10	8.04
41	7.99	7.98	8.05	8.00	8.09	7.94	7.97

^aRef. [28]; ^bTest set compounds; ^cOutlier; ^dNot determined.

Table 4: PLS and MLR-like PLS models from the descriptors of six-parameter CP-MLR models for the 5-HT₇ binding affinity

A: PLS equation			
PLS components		PLS coefficient (s.e.) ^a	
Component-1		-0.159(0.029)	
Component-2		-0.186(0.035)	
Component-3		-0.160(0.038)	
Component-4		-0.203(0.056)	
Component-5		0.217(0.075)	
Constant		8.493	
B: MLR-like PLS equation			
S. No.	Descriptor	MLR-like coefficient (f.c.) ^b	order
1	PW2	1.176(0.267)	1
2	VEA1	-0.381(-0.086)	4
3	BEHm4	-0.332(-0.075)	5
4	GGI9	-0.718(-0.162)	3
5	JGI5	0.116(0.026)	8
6	MATS6e	-0.288(-0.065)	6
7	GATS2v	-0.033(-0.007)	10
8	GATS4e	-0.108(-0.024)	9
9	nCs	1.064(0.241)	2
10	nCONHR	0.188(0.042)	7
	Constant	7.147	
C: PLS regression statistics			Values
n			30
r			0.894
s			0.288
F			19.158
Q ² _{LOO}			0.669
Q ² _{LSO}			0.696
r ² _{Test}			0.596

^aRegression coefficient of PLS factor and its standard error. ^bCoefficients of MLR-like PLS equation in terms of descriptors for their original values; f.c. is fraction contribution of regression coefficient, computed from the normalized regression coefficients obtained from the autoscaled (zero mean and unit s.d.) data.

Figure 1: Plot of the observed versus calculated pK_i values of oxindole derivatives

Figure 2: Plot of fraction contribution of MLR-like PLS coefficients (normalized) of the 10 descriptors (Table 4) to the activity

CONCLUSION

In conclusion, the present study has provided structure–activity relationships of the binding affinities of oxindole derivatives to 5-HT₇ receptor in terms of structural requirements. The binding affinity has, therefore become the function of the cumulative effect of different structural features which were identified in terms of individual descriptors. In order to improve the 5-HT₇ receptor binding affinity of a compound higher value of molecular topology and symmetry accounting parameter path/walk 2- Randic shape index (descriptor PW2) and lower value of eigenvector coefficient sum from adjacency matrix (descriptor VEA1) are favorable. Presence of more number of sp³ hybridized secondary carbon atoms (descriptor nCs) and secondary aliphatic amides (descriptor nCONHR) in a molecule will be supportive to the activity. The associations of masses to the eigenvalue n.4 of Burden matrix (BEHm4), van der Waals volume to path length 2 of Geary autocorrelation

(GATS2v) and Sanderson electronegativity to path length 6 of Moran autocorrelation (MATS6e) and path length 4 of Geary autocorrelation (GATS4e) have shown the prevalence of atomic properties and charge content in terms of 9th and 5th order topological and mean topological charge indices (GGI9 and JGI5) to explain the binding affinity. The PLS analysis has also confirmed the dominance of information content of the CP-MLR identified descriptors. The derived models and participating descriptors in them have suggested that the substituents of oxindole moiety have sufficient scope for further modification.

ACKNOWLEDGEMENT

Authors are thankful to their Institutions for providing necessary facilities to complete this study. Manju Choudhary is thankful to the Council of Scientific and Industrial Research (CSIR), New Delhi, India for provision of a senior research fellowship.

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Cite this article as:

Choudhary Manju and Sharma Brij Kishore. CP-MLR directed QSAR rationales for the activity profile of (Phenylpiperazinyl-alkyl) oxindoles as 5-HT₇ receptor ligands. Int. J. Res. Ayurveda Pharm. 2015;6(4):524-536 <http://dx.doi.org/10.7897/2277-4343.064100>

Source of support: Council of Scientific and Industrial Research (CSIR), New Delhi, India, Conflict of interest: None Declared

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